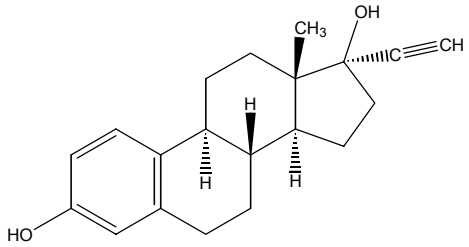
ESTROGENS (NOT CONJUGATED)

ETHINYLESTRADIOL
CAS No. 57-63-6

First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Ethinylestradiol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered in the diet, ethinylestradiol increased the incidence of pituitary tumors and malignant mammary tumors in mice of both sexes; malignant tumors of the uterus and cervix in female mice; and benign gonadal tumors in male mice. Oral administration of ethinylestradiol to rats increased the incidence of liver neoplastic nodules and pituitary chromophobe adenomas in both sexes, mammary tumors in males, and malignant liver tumors in females (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). When implanted as a pellet, ethinylestradiol induced mammary adenocarcinomas in 90% of rats given 1 mg; concomitant exposure to X-rays synergistically increased the number of tumors per rat and shortened the latency period of the tumors (IARC S.4, 1982; IARC S.7, 1987).

In other studies, ethinylestradiol administered orally in combination with certain progestins induced increased incidences of malignant tumors of the uterus, pituitary tumors, and hepatomas in female mice, and benign and/or malignant mammary tumors in male rats (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). Subcutaneous injection of an ethinylestradiol mixture induced mammary fibroadenomas in female rats (IARC V.21, 1979).

There is inadequate evidence for the carcinogenicity of ethinylestradiol in humans (IARC S.4, 1982). There is sufficient evidence for the carcinogenicity of steroidal estrogens in humans. Case reports and epidemiological studies of humans given ethinylestradiol alone were not available to IARC Working Groups (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982; IARC S.7, 1987). However, the use of oral contraceptives containing ethinylestradiol in combination with progestins is associated with an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease, endometrial cancer, and ovarian cancer. Epidemiologic studies also suggest that the administration of estrogens alone is strongly associated with an increased incidence of endometrial carcinoma in humans, and there is no evidence that ethinylestradiol is different from other estrogens in this respect. An IARC Working Group concluded that in the absence of adequate data on humans, it is reasonable to regard ethinylestradiol as if it presented a carcinogenic risk to humans (IARC V.21, 1979).

PROPERTIES

Ethinylestradiol occurs as fine white needles. It is practically insoluble in water, and soluble in ethanol, diethyl ether, acetone, dioxane, chloroform, vegetable oils, and solutions of fixed alkaline hydroxides. Ethinylestradiol is available in the United States as a grade containing 97%-102% active ingredient on a dried basis.

USE

The most widespread use of ethinylestradiol is in oral contraceptives. Ethinylestradiol is one of the most active steroidal estrogens known when administered orally (IARC V.21, 1979). It not only is used as the estrogen component in progestin-estrogen combination therapy and progestin-estrogen sequential therapy but also is used in estrogen treatment alone (IARC V.6, 1974). Additionally, ethinylestradiol is used in human medicine to treat conditions such as amenorrhea, breast carcinoma, hypogonadism, menopausal disorders, postpartum breast engorgement, and prostatic carcinoma; in such applications, it sometimes is used in combination with androgens or progestins (IARC V.6, 1974).

Ethinylestradiol is not used as a growth promoter in animals. It is used in veterinary medicine for estrogenic hormone therapy (IARC V.6, 1974).

PRODUCTION

The USITC does not identify any producers for ethinylestradiol. The 1998 Chemical Buyers Directory, however, lists three U.S. suppliers of the compound (Tilton, 1997). The 1984 Chem Sources Directory identified two domestic companies as manufacturers (Chem Sources, 1984). In 1983, U.S. imports of ethinylestradiol totaled 82 lb (USITCa, 1984). The 1979 TSCA Inventory reported one U.S. importer of ethinylestradiol in 1977, but no volume of imports (TSCA, 1979). Total U.S. sales of ethinylestradiol for use in human medicine in the mid-1970s were estimated to be less than 110 lb annually (IARC V.6, 1974). Commercial production of the compound in the United States was first reported in 1945 (IARC V.21, 1979).

EXPOSURE

The primary routes of potential human exposure to ethinylestradiol are ingestion, inhalation, and dermal contact. In 1977, estimates indicated that more than 80 million women were exposed to ethinylestradiol through the regular use of oral contraceptives. In 1972 estimates indicated that only 41 to 48 million women were exposed similarly to the compound (IARC V.21, 1979). Potential occupational exposure to ethinylestradiol may occur through inhalation and dermal contact. A joint investigation of an oral contraceptive plant, conducted by NIOSH and CDC, found evidence of hyperestrogenism among male and female workers. Blood tests showed 60% higher elevations of estrogens among employees who handled the powdered product; air samples of estrogen and progesterone varied widely (Drug Cosmet. Indust., 1977). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 2,770 people were potentially exposed to ethinylestradiol in the workplace in 1970, and 1,230 workers were potentially exposed in 1974. These estimates were based only on observations of the actual use of the compound and tradename products containing the compound (NIOSH, 1976). The National Occupational Exposure Survey (1981-1983) estimated a total of 97 workers, including 62 women, potentially occupationally exposed to ethinylestradiol

(NIOSH, 1984). Another source of potential human exposure is the residue of ethinylestradiol found in foliage, soil, water samples, and some drinking water (IARC, V.21, 1979).

REGULATIONS

Because ethinylestradiol is used as a pharmaceutical and in low quantities relative to other chemicals, it is not regulated by EPA. However, there may be a small pollution problem relative to hospital wastes. FDA regulates ethinylestradiol under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA has ruled that estrogens for general use must carry patient and physician warning labels concerning use, risks, and contraindications (has been extended to all oral contraceptives). OSHA regulates ethinylestradiol under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-61.